EXHIBIT A

J Immunol. 1985 Aug;135(2 Suppl):843s-847s. Related Articles, Links

The contribution of neurogenic inflammation in experimental arthritis.

Levine JD, Moskowitz MA, Basbaum AI.

The release of the peptide neurotransmitter substance P from the peripheral terminals of nociceptive afferent neurons and the release of catecholamines from postganglionic sympathetic efferent neurons produce physiologic changes associated with acute inflammation. The contribution of these neurogenic mechanisms to inflammatory diseases has not been determined. Activation of central neural circuits elicits similar physiologic changes, and lesions of the peripheral and central nervous system are associated with alteration in activity of inflammatory diseases. We have evaluated the contribution of neurogenic inflammation to the severity of joint injury in experimentally induced arthritis in the rat. The finding of a greater density of substance P-containing nociceptive afferents in a joint that develops more severe arthritis (ankle) suggests a role of substance P in joint injury. Direct evidence that the proinflammatory factor released from these nociceptors is substance P is provided by the finding that the injection of substance P into a joint which normally develops less severe arthritis (knee) increases the severity of arthritis in that joint. A contribution of catecholamines to the severity of joint injury was suggested by the finding that both guanethidine-induced sympathectomy and reserpine-induced depletion of catecholamines attenuated the severity of joint injury. Finally, a contribution of central neural circuits to inflammatory processes was studied in a model in which activation of nociceptive afferents elicited swelling and tenderness at a remote site. This reflex neurogenic inflammation was inhibited by intracerebroventricular injections of morphine, which also attenuated the severity of arthritis. These studies provide evidence that elements of the peripheral afferent and sympathetic efferent neurons and of descending supraspinal, opioid-mediated, circuits in the central nervous system modulate the severity of joint injury in experimental arthritis in the rat.